Non-Disjunction of Chromosome 21 in the Young Mother at Conception

Hala Ahmed ElGindy¹, Magd Ahmed Kotb¹, Mohamed Farouk Mohamed¹, Walaa Alsharany Abuelhamd¹, Nahed Naguib Alsabagh², Nancy Anis³, Aly Elkazaz¹*

¹ Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt; elgindyhala@gmail.com, magdkotb@karakainy.edu.eg, m.farouk76@gmail.com, walaa1@gmail.com
² Department of Pediatrics, Ministry of Health Hospitals, Department of Pediatrics, Ministry of Health Hospitals, Fawzy Moaz Pediatric Hospital, Alexandria, Egypt; nahedalasabagh@yahoo.com
³ Department of Cardiology, School of Medicine, National University in Ireland, Galway, Ireland; nancy.anis@nuigalway.ie

* Correspondence: alyelkazaz1@gmail.com
Received: 5/6/2022; Accepted: 18/6/2022; Published online: 1/7/2022

Abstract:

Background: Maternal age influences the type of chromosomal anomaly in Down syndrome. The older age is associated with non-disjunction while the younger age is associated with translocation of chromosome 21.

Aim of the Work: To study the cytogenetics of children with Down syndrome born to the young mother who presented to Pediatrics Genetics Unit at Cairo University Children Hospital during one year (2019), and compare with those born to an older mother.

Materials and Methods: This descriptive retrospective study analyzed records of 210 children with Down syndrome who presented to Pediatrics Genetics Unit at Cairo University Children Hospital during 2019.

Results: Among the total 210 studied children with Down syndrome, 21 (10%) were born to young mothers aged 21 years or less at conception. Seven (33.34%) were males and 14 (66.66%) were females. Twenty (95.2%) were first born to a young mother, only 1 was a second born. Karyotyping proved that 6 (28.6%) had Robertsonian translocation of trisomy 21, and 15 (75.4%) had non-disjunction. Only 1 (4.76%) of children born to younger mothers had associated cardiac anomalies, while among those born to the older mother 40 (21%) had associated anomalies, of them were cardiac 36 (19.04%), hydrocephalus in one (0.5%), and ambiguous genitalia in 3 (1.58%) (p=0.072). First born trisomy 21 were 109 (51.9%) among the whole studied cohort, with a mean maternal age ± SD of 30.2 years ± 7.35 years, their karyotyping was non-disjunction, Robertsonian translocation and mosaic in 100, 5 and 3 respectively. Cardiac anomalies were encountered among 18 (16.5%).

Conclusion: Children born with trisomy 21 to mothers younger than 21 at conception are mostly due to non-disjunction. First born children with trisomy 21 comprised half the studied cohort of trisomy 21. Further studies to define preventable causes of non-disjunction in the young mother, are needed to reduce the incidence of Down syndrome.

Level of Evidence of Study: II B. (I)

Keywords: Down syndrome; non-disjunction; young mother; trisomy 21.

Abbreviations: ASD: Atrial septal defect; CAV: complete atrioventricular canal; VSD: ventricular septal defect.

Introduction

It has been long noted that maternal and paternal age advancement is associated with increased risk of non-disjunction trisomy 21 off-springs (2, 3). Trisomy 21 or Down syndrome is a common numerical chromosomal anomaly. Survival of afflicted subjects is ever increasing from 10 years of those with Down syndrome in the 1960s to almost 47 years in 2007. Hence, the increased prevalence of Down Syndrome, and the growing need to address their medical and
social needs for smooth integration in society (4, 5). Parents age advancement is noted in highly educated societies compared to other less educated societies (6–9). With the noted advancement of parental age and the increased risk of non-disjunction, it is less expected to come across young mothers. As only one trisomy is expected for every 1,250-2000 in a woman who conceives at age 25, compared to 1 in a hundred who conceives at 40 years (10). Cytogenetics and karyotyping allows delineation of the chromosomal anomaly underlying the trisomy 21 among children with Down Syndrome. The trisomy 21 in a baby born to a young mother is more likely attributed to translocation carriage or mosaicism, than in the older mother (11, 12). The aim of this work is study the cytogenetics of children with Down syndrome born to the young mother who presented to Pediatrics Genetics Unit at Cairo University Children Hospital during one year (2019), and compare with those born to an older mother.

Subjects and Methods

This retrospective cohort study involved data of 210 children with Down Syndrome following up at the Pediatrics Genetics Unit, Children Hospital, Cairo University Hospitals during one year (2019). The study was approved by the Ethical Committee of Cairo University Pediatric Department and Higher Education Research Committee of Faculty of Medicine, Cairo University, Egypt. An informed consent was obtained from the patients’ parents.

All data of children with Down Syndrome with mothers aged 21 and 9 months or less years at birth were included in the study. Data of those with higher maternal age was used for comparison.

Methods

- Data Collection:
  Of all relevant clinical features, maternal age, family history, parental consanguinity, investigations and associations if any.

- Karyotyping
  1. **Culture and Harvesting**: A total 0.5 ml of blood sample was culture in 5ml RPMI 1640 (gibco ready to used media) in a 15ml screw cap culture vials with aseptic precautions. Incubation was done in CO2 incubator at 37°C, 5% CO2 inject and 84% humidity (Incubator values set) for 70 hours.
  2. **Banding (Trypsin Digestion)** in Giemsa solution for 5 to 7 minutes. The slides were mounted with coverslip using distyrene, a plasticizer, and xylene (DPX) solution.
  3. **Metaphase Analysis**: 20-25 metaphases were examined and 3- 5 cells were photographed and karyotyped. In case of mosaicism, 50 to 100 metaphases were scored. Karyotype description was done according to the international nomenclature guidelines (ISCN) (13).

Statistical Analysis

All data was tabulated and analyzed using Statistical Package for Social Sciences (SPSS) (version 20). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ2) and Fisher exact was used to calculate difference between qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation) and/or median and range. Mann Whitney test was used to calculate difference between quantitative variables in the two groups for non-parametric variables. All statistical comparisons were two tailed with significance level of p value ≤ 0.05.

Results

The median of age of referral of Down syndrome are 4 months with range between 1 to 150 months, while the median of their mothers was 34 years with range between 17 to 47 years. The studied group comprised 210 children with Down, of them 107 (51.9%) were males, mostly 1st sibling (51.4%), mostly from Urban areas (57.6%), 29.5% with positive parental consanguinity, and only 8.1% with history of same condition in the family as presented in table 1. Among the total 210 studied children with Down syndrome, 21(10%) were born to young mothers aged 21 years or less at conception. Table 1 shows the characteristics of trisomy 21 according to maternal
age at conception of the mothers younger than 21 at conception. Seven (33.34%) were males and 14 (66.6%) were females. Twenty (95.2%) were first born to the young mother, only 1 was a second born. Karyotyping proved that 6 (28.6%) had Robertsonian translocation of trisomy 21, and 15 (75.4%) had non-disjunction.

**Table 1.** Demographic characteristics of Down syndrome (N=210).

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at referral</td>
<td>4.0</td>
<td>1-150</td>
</tr>
<tr>
<td>Mother Age</td>
<td>34</td>
<td>17-47</td>
</tr>
<tr>
<td>Variable</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>103</td>
<td>48.1%</td>
</tr>
<tr>
<td>M</td>
<td>107</td>
<td>51.9%</td>
</tr>
<tr>
<td>1st</td>
<td>108</td>
<td>51.4%</td>
</tr>
<tr>
<td>2nd</td>
<td>43</td>
<td>20.4%</td>
</tr>
<tr>
<td>3rd</td>
<td>43</td>
<td>20.4%</td>
</tr>
<tr>
<td>4th</td>
<td>14</td>
<td>6.6%</td>
</tr>
<tr>
<td>5th</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Sibling order</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>89</td>
<td>42.4%</td>
</tr>
<tr>
<td>Urban</td>
<td>121</td>
<td>57.6%</td>
</tr>
<tr>
<td>Positive consanguinity</td>
<td>62</td>
<td>29.5%</td>
</tr>
<tr>
<td>History of same condition in the family</td>
<td>17</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

**Table 2.** Trisomy 21 characteristics according to maternal age up to 21 years old at conception among 21 studied children.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Order among sibs</th>
<th>Positive Parental Consanguinity</th>
<th>Associated Congenital Anomalies</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>Males</td>
<td>Number</td>
<td>Type</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-disjunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age at conception: up to 16 years (total 2 children)</td>
<td>2</td>
<td>0</td>
<td>First</td>
<td>2</td>
</tr>
<tr>
<td>Maternal age at conception: 18 years (total 1 children)</td>
<td>1</td>
<td>0</td>
<td>First</td>
<td>1</td>
</tr>
<tr>
<td>Maternal age at conception: &gt; 18 years up to 19 (total 2 children)</td>
<td>2</td>
<td>0</td>
<td>First</td>
<td>2</td>
</tr>
<tr>
<td>Maternal age at conception: &gt;19 years up to 20 (total 5 children)</td>
<td>0</td>
<td>5</td>
<td>First</td>
<td>5</td>
</tr>
<tr>
<td>Maternal age at conception: &gt; 20 years up to 21 (total 11 children)</td>
<td>2</td>
<td>9</td>
<td>First</td>
<td>10</td>
</tr>
</tbody>
</table>

*There was family history of Down syndrome in the family. R. Translocation: Robertsonian translocation; VSD: ventricular septal defect.*

Table 2 shows the characteristics of children with trisomy 21 born to mothers older than 21 at conception. There was no difference among those born to the younger mother and the older mother as regards the dysmorphic features hypertelorism, multiple dysmorphic features, broad nasal bridge, prominent occiput, large tongue-silky hair, low set ear, protruded tongue, silky hair-large tongue, depressed nasal bridge, high arched palate and upward slanting eye. Only 1 (4.76%) of children born to younger mothers had associated cardiac anomalies, while among those born to the older mother 40 (21%) had associated anomalies, of them were cardiac 36 (19.04%), hydrocephalus in one (0.5%), and ambiguous genitalia in 3 (1.58%) (p=0.072). First born trisomy 21 were 109 (51.9%) among the whole studied cohort, with a mean maternal age +/- SD of 30.2 years +/- 7.35 years, their karyotyping was non-disjunction, Robertsonian translocation and mosaic in 100, 5 and 3 respectively. Cardiac anomalies were encountered among 18 (16.5%).


https://cupsj.journals.ekb.eg/
Table 3. Trisomy 21 characteristics according to maternal age above 21 year old at conception among 189 studied children.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Order among sibs</th>
<th>Positive Parental Consanguinity</th>
<th>Associated Congenital Anomalies</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>Males</td>
<td>Number</td>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Maternal age at conception: above 21 up to 25 years (total 24 children)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>11</td>
<td>First</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Maternal age at conception: &gt; 25 years up to 29 (total 29 children)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>12</td>
<td>First</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Maternal age at conception: &gt; 29 years up to 34 (total 53 children)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>34</td>
<td>First</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fourth</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maternal age at conception: &gt; 34 years up to 39 (total 68 children)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>34</td>
<td>First</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fourth</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fifth</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maternal age at conception: &gt; 39 years up to 45 (total 15 children)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>First</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fourth</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fifth</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

ASD: Atrial septal defect; CAV: complete atroioventricular canal; R. Translocation: Robertsonian translocation; VSD: ventricular septal defect

Discussion

Ten percent of our studied children with trisomy 21 were born to mother who were younger than 21 at conception. Of them 75% were attributed to non-disjunction. Maternal age advancement was always noted to be associated with trisomy 21(14). It was attributed to a multifactorial trait that results in failure of chromosomes to segregate during meiosis. Yet, non-age related non-disjunction was reported in those with a single pericentromeric exchange in first meiotic division (15). We did not study the maternal failure of separation of the homologous chromosomes in first meiotic division and did not study maternal failure of sister chromatids to separate during meiosis II, stratified by maternal age. We did not study the mitotic failure of sister chromatids to separate as well. We did not study the epigenetic and environmental factors that might be responsible for this non-disjunction in the offspring of the younger mother (16).

The phenotype of those born to the younger mother and the older mother was not different. There was no peculiarity of dysmorphic features in either group. Yet, there was more associated anomalies in the trisomy 21 born to the older mother, that did not mount to statistical significance, with a total of 37 (17.6%) children having cardiac anomalies. The burden of trisomy
21 is not limited to the family and society only, the associated anomalies pauses other loads on other departments as cardiology and cardiosurgery, etc.

The first born child with trisomy 21 was encountered among more than half our studied cohort. Their mothers had a higher mean age at conception of 30 years +/- 7 years. The trisomy 21 is as common in first born to the older mother as in the later pregnancies of the older mother who had her earlier off spring in a younger age. It seems that advancement of age is the crucial factor that paves the way for environmental factors and epigenetic factors to interplay (16).

The lack of phenotype and the majority of non-disjunction, limit prenatal diagnosis to translocation carriers, and highlight the importance of Down syndrome diagnosis during early pregnancy. Sensitivity and specificity of tests for diagnosis of Down syndrome as detection of fetal nuchal translucency, the pregnancy associated plasma protein-A, free human choriocarcin gonadotropin in maternal blood, cell-free fetal DNA second-generation sequencing technology in maternal blood are 17.85% and 85.71%, 62.50% and 87.35%, 58.93% and 86.62% (17) and 97% and 99% (18) respectively. The later relies on sequencing of fetal cells and fetal stem cells that traffic into the maternal circulation during pregnancy.

The incidence of Down syndrome in Egypt is 1:555 and 1:770 life births (19). We recommend establishment of a registry of cases with trisomy 21 all over Egypt. Studies of cost-effectiveness of the highly sensitive non-invasive sequencing tests are needed, yet with the advancement of technology and its availability, we support its routine use during pregnancy of the advanced in age parents, and if possible among all pregnancies even among the younger mother. Prenatal screening for Down syndrome is vital to reduce the disease burden of Down syndrome, and reduce the burden of mental sub-normality, associated anomalies, etc.

A limitation of this study is that we did not study influence of advancing paternal age on the type of trisomy 21, as the paternal contribution to trisomy 21 in the offspring is 50% when maternal age is above 35 (20). Again we did not study the potential causes of the non-disjunction among our studied cohort. We did not study inactivation of topoisomerase II, separase or condensin (21) that are potential causes for non-disjunction as they were beyond the scope of the study.

Conclusion

Children born with trisomy 21 to mothers younger than 21 at conception are mostly due to non-disjunction. First born children with trisomy 21 comprised half the studied cohort of trisomy 21. Further studies to define preventable causes of non-disjunction in the young mother, are needed to reduce the incidence of Down syndrome. Multidisciplinary medical, counseling, family planning and social support for young parents of the Down syndrome are vital.

Author Contributions

All authors searched medical literature, databases, conceptualized, conducted the case review and reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING

Authors declare there was no extramural funding provided for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

References


© 2022 submitted by the authors. Open access publication under the terms and conditions of the Creative Commons Attribution (CC-BY-NC-ND) license. (https://creativecommons.org/licenses/by-nc-nd/2.0/).